REMARKS

Please replace the paper copy and the computer readable form copy (CRF copy) of the Sequence Listing submitted for this application on July 6, 2000, with the substitute paper copy and CRF submitted herewith. Applicants have amended the Sequence Listing to add to it sequences in the application as filed.

The Specification has been amended to include sequence identification numbers which were omitted at the time of filing and to amend the five pages of Figure 6 to label separately and distinctly each page as Figure 6A-6E.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**".

The undersigned hereby states that the paper copy of the Sequence Listing and the computer readable form copy of the Sequence Listing, submitted in accordance with 37 C.F.R. § 1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the Sequence Listing into the above-captioned case is respectfully requested.

In the unlikely event that the patent office determines that extensions and/or other relief is required, applicant petition for any required relief including extensions of time and authorize the assistant commissioner to charge the cost of such petitions and/or fees due to our deposit account no. 03-1952 under order no. 381092000721. The assistant commissioner is not authorized to charge the cost of the issue fee to the deposit account.

Respectfully submitted,

Date: January 13, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning on page 3, line 28 has been amended as follows:

As described in Stea, A., *et al.* (1994) (supra), the α_1 subunits are generally of the order of 2000 amino acids in length, ranging from 1873 amino acids in α_{1S} derived from rabbit to 2424 amino acids in α_{1A} derived from rabbit. Generally, these subunits contain 4 internal homologous repeats (I-IV) each having six putative alpha helical membrane spanning segments (S1-S6) with one segment (S4) having positively charged residues every 3rd or 4th amino acid. There are a minority of a splice variant exceptions. Between domains II and III there is a cytoplasmic domain which is believed to mediate excitation-contraction coupling in α_{1S} and which ranges from 100-400 amino acid residues among the subtypes. The domains I-IV make up roughly 2/3 of the molecule and the carboxy terminus adjacent to the S6 region of domain IV is believed to be on the intracellular side of the calcium channel. There is a consensus motif (QQ-E-L-GY-WI-E) (SEQ ID NO:44) in all of the subunits cloned and described in Stea, A., *et al.* (supra) downstream from the domain I S6 transmembrane segment that is a binding site for the ß subunit.

The paragraph beginning on page 6, line 7 has been amended as follows:

Figure 6A-6E shows the nucleotide and deduced amino acid sequence of human T-type calcium channel α_{1G}.

The paragraph beginning on page 7, line 6 has been amended as follows:

One distinguishing feature of the α1G, α1H and α1I T-type channels over other types of calcium channels and sodium channels is that the pore region (P-region) in each of the four structural domains contains a diagnostic amino acid sequence implicated in channel

permeability. Figure 8 shows that the T-type channels contain the residues glutamate/glutamate/aspartate/asparate (single letter amino acid code: EEDD(SEQ ID NO:45)) in the P-regions of domains I-IV. In contrast, figure 8 shows that in sodium (Na) channels the P-region of the four domains contains the residues: aspartate/glutamate/lysine/alanine (single letter amino acid code: DEKA (SEQ ID NO:46)), while high threshold calcium channels such as the L-type channel contain the residues: glutamate/glutamate/glutamate/glutamate (single letter amino acid code: EEEE (SEQ ID NO:47)). The α1G, α1H and α1I T-type channels are also distinct in this region compared to other types of ion channels including the *C. elegans* C11D2.6 and C27F2.3 and the rat NIC-channel (Figure 8).

The paragraph beginning on page 7, line 18 has been amended as follows:

A second distinguishing characteristic of the α_{1G}, α_{1H} and $\alpha 1_I$ T-type channels compared to other types of calcium channels is that they do not contain a β subunit binding consensus sequence in the cytoplasmic linker separating domains I and II. In contrast, all high threshold calcium channels contain a consensus sequence (single letter amino acid code: QQ-E--L-GY--WI---E) (SEQ ID NO:44) shown to physically interact with the calcium channel β subunit (Pragnell, M., De Waard, M., Mori, Y., Tanabe, T., Snutch, T.P. & Campbell, K.P., 1994, Nature 368:67-70). Thus it appears the presence of a β subunit does not modify activity, nor is its presence required.

The paragraph beginning on page 8, line 5 has been amended as follows:

Alternatively, the T-type α_1 subunit molecules can be defined by homology to the human and rat nucleotide and amino acid sequences described herein. Thus, T-type α_1 subunits will typically have at least 50%, preferably 70% homology in terms of amino acid sequence or encoding nucleotide sequence to the sequences set forth in SEQ ID NOS. 23-28 herein or those shown in Figure 6A-6E. Preferably, the homology will be at least 80%, more preferably 90%, and most preferably 95%, 97%, 98% or 99%.

The paragraph beginning on page 8, line 11 has been amended as follows:

Relative homology may also be defined in terms of specific regions; as set forth above, certain regions of T-type channel α_1 subunits have very high homologies while other regions, such as the cytoplasmic region between domains II and III have less homology. Thus, T-type α_1 subunits will have over 75% homology; preferably over 85% or over 95% homology, more preferably over 98% homology in domains I-IV to those of SEQ. ID. NOS. 23-28 or Figure 6A-6E. The degree of homology in the cytoplasmic region between domains II and III may be substantially less, *e.g.*, only 25% homology, preferably, 50% homology or more preferably 60% homology. Similarly, the intracellular region downstream of domain IV may be less homologous than within domains I-IV.

The paragraph beginning on page 11, line 24 has been amended as follows:

Following these protocols, full length mammalian α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs were isolated by using the 567 base pair human fragment (SEQ. ID NO. 19) to screen a rat brain cDNA library. Sequencing of the recovered sequences identified the three distinct classes of calcium channel subunits which have been denominated herein as α_{1G}, α_{1H} and α_{1I} subunits. For each class of subunit, complete sequencing of the largest cDNA confirmed that it represented only a portion of the predicted calcium channel coding region. Complete sequences for the three new subunits were obtained by rescreening the rat brain cDNA library with probes derived from the partial length cDNAs to obtain overlapping segments. These segments were combined to form a complete gene by restriction digestion and ligation. The complete cDNA sequences of the rat α_{1G}, α_{1H} and α_{1I} subunits are given by SEQ. ID NOS. 23, 25 and 27, respectively. Corresponding amino acid sequences are given by SEQ. ID NOS. 24, 26 and 28. The same techniques are employed to recover human sequences by screening of a human or other mammalian library. Thus, for example, partial length human sequences for α_{1G} and α_{1H} T- type calcium channels have been recovered using the same probe (SEQ. ID NO. 19) and the

full length rat α_{1I} cDNA (SEQ. ID. NO. 27) has been used to recover a partial length DNA encoding a human α_{1I} T-type calcium channel. The DNA and amino acid sequences for these partial length human calcium channels are given by SEQ. ID NOS. 30-35. A complete coding sequence for human α_{1G} was also obtained and is set forth, along with the deduced amino acid reference, in Figure 6A-6E.

The paragraph beginning on page 22, line 17 has been amended as follows:

The remaining region of the 3' α_{1G} subunit cDNA was obtained using the PCR method on a human thalamus cDNA library with primers MD19-sense (5'GCG TGG AGC TCT TTG GAG 3') (SEQ ID NO:48) and G26- antisense (5' GCA CCC AGT GGA GAA AGG TG 3') (SEQ ID NO:49). The PCR protocol used was 94°C –30 sec, 58°C –30 sec, 72°C –30 sec for 25 cycles (Bio-rad Gene Cycler). A cDNA fragment of 1617 bp was subcloned into p-Gem-T-Easy plasmid vector (Promega) and sequenced. The 3'PCR cDNA was identified as a human α_{1G} subunit spanning from Domain IV-S5 to the carboxyl terminus including the stop codon.

The paragraph beginning on page 22, line 28 has been amended as follows:

The complete nucleotide and amino acid sequences are shown in Figure 6A-6E.